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Mariah Smith

Philadelphia College of Osteopathic Medicine, MariahSm@pcom.edu

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**Are Proton Pump Inhibitors a Safe and Effective Treatment
for Gastroesophageal Reflux Disease in Infants Less Than
Twelve Months Old?**

Mariah G. Smith, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: The objective of this systematic review is to determine whether or not proton pump inhibitors are a safe and effective treatment for gastroesophageal reflux disease in infants less than twelve months old.

STUDY DESIGN: Review of three English language primary studies published in 2003, 2007, 2009

DATA SOURCES: Randomized, double blind, placebo controlled trials comparing proton pump inhibitors to placebo were found using Ovid MEDLINE, and Cochrane databases.

OUTCOMES MEASURED: Gastroesophageal reflux disease symptoms in infants. Symptoms include crying, irritability, vomiting, apnea, bradycardia, choking, and behavioral trials. One trial used responder status, which is defined as a $\geq 50\%$ reduction from baseline in either percentages of feedings with crying episodes or duration (in minutes) of episodes averaged across feedings. Another trial documented the cry/fuss time in minutes per 24 hour period. Other outcomes include adverse events requiring treatment and serious adverse events requiring hospitalization.

RESULTS: All three RCTs included in this review found that proton pump inhibitors were not effective in reducing the symptoms of GERD in infants. There was no significant decrease compared to control groups. One RCT showed a significant increase in the number of both adverse events and serious adverse events compared to placebo groups.

CONCLUSIONS: Results of the RCTs reviewed demonstrate that proton pump inhibitors are not a safe and effective treatment for gastroesophageal reflux disease in infants less than twelve months old. Further research is warranted to determine the primary cause of these reflux symptoms and to investigate transient lower esophageal sphincter relaxation.

KEY WORDS: proton pump inhibitors, infants

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common disorder affecting persons of all ages and is characterized by reflux of the gastric contents into the esophagus, causing complications. Many infants under the age of one, including premature infants, experience symptoms attributed to GERD. The principal treatment for symptomatic GERD in adults and children is acid suppression. Proton pump inhibitors (PPI) have widespread use in adults and children and are recognized as the most effective agents to suppress gastric acid secretion². Although FDA indication for PPI use does not include patients less than one year old, there has recently been an increasing amount of PPIs used for this age group to alleviate symptoms¹.

GERD in infants is of major relevance to the scope of physician assistant practice. Excessive crying is the most common reason for parents to seek medical help for newborns in the first three months of life². It is hypothesized that gastroesophageal reflux is a frequent cause of this irritability and crying. While GERD is usually a benign process in infants, significant irritability of the child leads to increased concern of the parent and more frequent medical visits and costs. If the irritability of the infant is related to reflux, then reduction in acid exposure by highly effective proton pump inhibitors should reduce the symptoms. This logical hypothesis has been put into practice, as demonstrated by the seven-fold increase in the use PPIs in infants between 1999 and 2004¹. Because there is no FDA indication for PPI use in infants, the actual amount of money spent on “off-label” use of PPIs for this population is not well-documented or readily available.

GERD is defined as symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus. The clinical symptoms of GERD in an infant differ from

symptoms of an adult. The most common symptom of GERD in an infant is regurgitation/vomiting⁴. The additional symptoms in an infant are non-specific and include excessive irritability and crying, failure to thrive, feed refusal, apnea, or aspiration pneumonia. Preterm infants and newborns are at increased risk for GERD due to their immature musculature, predominantly liquid diet and supine positioning while feeding. The principal mechanism of acid reflux in infants is found to be transient lower esophageal sphincter relaxation³. Moreover, GERD in infants is associated with the development of serious chronic health issues such as recurrent pneumonia, chronic cough, recurrent stridor and reactive airway disease⁴.

The goals of therapy for GERD are to relieve symptoms, promote healing of esophagus, and to prevent respiratory complications and recurrence of the disease. Treatment of GERD in children and adults includes antacids, pro-kinetic agents, and acid suppressants, such as histamine H₂ receptors and PPIs. Currently there are no therapies that target the transient relaxation of the lower esophageal sphincter. In children over the age of one it has been found that PPIs have superior efficacy over other treatments⁴. Because no PPIs are approved for usage in infants, conservative treatments and non-pharmacological management are attempted initially. Feeding strategies include the use of thickened or hypoallergenic formulas, frequent burping, frequent small feedings, or dairy avoidance by breast-feeding. Because there is an increase in reflux when supine, parents are encouraged to try to minimize supine positioning and vigorous handling post-feeding. Additional simple conservative measures include increased parental reassurance and smoking cessation¹.

While the above treatments may be effective, many infants do not respond to conservative treatments. PPIs may provide satisfactory reduction of symptoms of GERD in infants over other products and methods. Based on the findings that PPIs are the most

efficacious GERD agents and that they are preferred treatment for children older than one, it is proposed that they will be effective treatments in infants. Health care providers have been recommending and prescribing PPIs for infants in an escalating amount. However, there is a lack of sufficient evidence and reputable randomized controlled trials that demonstrate the efficacy and safety of PPI use in this specific population.

OBJECTIVE:

The objective of this systematic review is to determine whether or not proton pump inhibitors are a safe and effective treatment for gastroesophageal reflux disease in infants less than twelve months old.

METHODS:

All three studies selected for this review met the following criteria. The population was otherwise healthy infants, including premature infants, who were less than twelve months of age. The interventions used in the studies were the administration of weight-based doses of proton pump inhibitors, namely omeprazole and lansoprazole. The main outcomes measured were reduction of GERD symptoms, such as cry/fuss time, irritability, vomiting, choking, apnea, as well as adverse events and serious adverse events. All of these outcomes qualify as patient oriented evidence that matters (POEM). The studies were double blind, randomized and placebo-controlled.

The author searched Ovid Medline and Cochrane Database of Systematic Reviews for articles and RCTs using the keywords “proton pump inhibitors” and “infants”. All articles in this review were in English and published in peer-reviewed journals. All articles were selected based on importance of outcomes to the patient (POEM). Inclusion criteria were studies that were

randomized, controlled, prospective, based on patient oriented outcomes, and published after 1996. Exclusion criteria were articles that were published before 1996 and articles that focused on patients over twelve months of age. The study performed by Orenstein et al took place at 16 centers, with 8 in the United States and 8 in Poland, between the dates of June 29, 2006 and May 16, 2007. The studies performed by Moore et al and Omari et al were both conducted in Australia. The statistics utilized in the studies were p values, number needed to harm (NNH), relative risk increase (RRI), and absolute risk increase (ARI).

OUTCOMES MEASURED:

The outcomes addressed in the Orenstein 2009 study were responder status, adverse events (AE) and serious adverse events (SAE). AEs were treatment emergent cases and SAEs required hospitalization. Responder status is defined to be >50% reduction from baseline in either percentages of feedings with crying episodes or duration (in minutes) of episodes averaged across feedings. Responder rate was the percentage of participants who were responders at week 4. Outcomes were measured by documenting the daily number and duration of crying episodes during or \leq 1 hour after feeding. AEs and SAEs were also documented.

The outcomes addressed in the Moore 2003 study were the cry/fuss time of the infant in a 24 hour period and the irritability of the child. The outcomes were measured by 1.) a diary in which the parents recorded infant behavior including crying and fussing time and 2.) a visual analog score (VA) ranging from 0-10 of parental impression of the level of infant irritability.

The outcomes addressed in the Omari 2007 study were symptom events that were recorded on bedside symptom charts by neonatal nursery staff. Symptom events were classified as vomiting, apnea, bradycardia, and behavioral changes.

Table 1: Demographics of included studies

Study	Type	#Pt	Age	Inclusion Criteria	Exclusion Criteria	WD	Intervention
Orenstein 2009 (1)	Double blind RCT	162	28 days to <12 months; preterm corrected age 44 weeks but <12 months	Weight >2.0 kg, daily diary documented crying during or within 1 hour \geq 25% of feeds during 4 days of randomization despite \geq 7 days of non pharmacologic management	Use of PPI in 30 days, use of H ₂ antagonists in 7 days, clinically significant disease, esophageal disease or upper GI anomaly, requirements of continuous tube feedings	64	Lansoprazole 1 x daily x 4 weeks. Dosages: 0.2 to 0.3 mg/kg/day for infants \leq 10 weeks of age; 1.0 to 1.5 mg/kg/day for infants >10 weeks of age
Moore, 2003 (2)	Double blind RCT	30	3-12 months in age	History of spilling, irritability and crying; previously given empirical treatment for GERD; 24 hour pH monitoring reflux index (total recording time with pH<4 in 24 hours) of >5%, biopsy criteria for esophagitis	Use of PPI before recruitment, history of melena or hematemesis, medical or surgical condition other than GERD	4	Omeprazole: Infants weighing 5-10 kg were given 10 mg daily x 2 weeks; infants >10 kg were given 10 mg BID x 2 weeks
Omari, 2007 (3)	Double blind RCT	10	Preterm infants, mean post menstrual age of 36.1 weeks, mean postnatal age 50 days	Preterm infants with symptoms of GERD who did not respond to conservative therapy, reflux index >5%	<32 weeks PMA, on CPAP or ventilation, acute illness, neurologic disease, hepatic/renal impairment, bone marrow abnormality	0	Omeprazole 0.7 mg/kg added to 2 mL/kg of antacid Mylanta given in NG tube to infant

RESULTS

The Orenstein 2009 study compared the efficacy of PPI lansoprazole versus placebo for the reduction of GERD symptoms as shown in Table 2. Lansoprazole and placebo produced identical responder numbers (54%). Both the relative benefit increase and absolute benefit increase are zero, which produced an unreal number for number needed to treat. Interestingly, responder rates were greater in patients who continued with non-pharmacological management into the double-blind period (63%) compared those who did not (19%). This study included rates for compliance with medication (93% for PPI vs. 95% for placebo) and diary recordings (96% PPI vs. 95% placebo).

Table 2: Efficacy of lansoprazole vs. placebo for reduction of GERD symptoms, Orenstein 2009

	Lansoprazole double-blind (≤ 4 weeks, n=81)*	Placebo double-blind, (≤ 4 weeks, n=81)*	P value	Lansoprazole open label (1-3 weeks, n=55)*
Primary efficacy: Responder rate, n (%)	44 (54%)	44 (54%)	NS	NA
Discontinued due to non-efficacy, n (%)	28 (35%)	29 (36%)	NS	0
Compliance				
$\geq 90\%$ for drug, % of subjects	93%	95%	-	98%
$\geq 90\%$ for daily diary, % of subjects	96%	100%	-	93%
Global Severity assessment §				
By parent: Improvement at week 4	45 (56%)	41 (51%)	NS	44 (80%)
By physician: improvement at week 4	44 (55%)¶	40 (49%)	NS	47 (85%)
Individual Symptoms				
Cry, % of feeds/ week	-20	-20	NS	-19
Regurgitate, % of feeds/ week	-14	-11	NS	-20
Stop feed soon, % of feeds/week	-7	-8	NS	-3
Feed refusal, % of days/week	-14	-10	NS	-15
Arching back, % of days/week	-20	-18	NS	-33
Coughing, % of days/week	0	-9	NS	-3
Wheezing, % of days/week	-5	-6	NS	-12
Hoarseness	2	-5	NS	-9

NS, not significant; NA, not applicable

*For subjects withdrawn from double-blind treatment before the 4th week, the last week of available data is carried forward to the 4th week for the individual symptoms and GAs. The open label treatment ranged from 1-3 weeks, depending on the time of withdrawal from the double-blind treatment; the final week of open label data is summarized.

§Improved at least 1 severity level compared to baseline assessment

¶Data missing from 1 subject: 44/80 (54%)

Assessing the safety of this drug class for this age group and population is a high priority of this systematic review. The Orenstein 2009 study demonstrated that there are some safety concerns, as illustrated in Table 3. There were more treatment emergent adverse events in the lansoprazole-treated subjects than the placebo group (62% vs. 46% respectively). Of the subjects who continued with open-label treatment with lansoprazole, 62% experienced AEs. AEs were mostly mild or moderate and include (in descending order of frequency of occurrence): upper respiratory infections, constipation and GERD, dermatitis and eczema, ear infections, fever, lower respiratory infections, respiratory tract congestion, rhinorrhea, candidiasis, diarrhea (excluding infective), vomiting, alkaline phosphatase increase, and viral infection. The p-value of 0.058 was deemed as not significant. The relative risk increase (RRI) and absolute risk increase (ARI) were 35% and 16%, respectively. The numbers needed to harm (NNH) is 7.

Serious AEs (SAEs) during the double-blind treatment were significantly more frequent in the lansoprazole group compared to placebo (12% vs. 2%). The p-value is 0.032 which indicates clinical significance. Number needed to harm is 10 patients and the RRI and ARI are 5% and 10%, respectively. All patients with SAEs were hospitalized and no deaths occurred. SAEs include the following medical conditions in descending order of frequency: lower respiratory infections, diarrhea, ileus, dehydration, ear infection (otitis media), upper respiratory infections, epididymal infection, arachnoid cyst, cellulitis, febrile convulsion, and *Klebsiella* infection. Orenstein et al reported that no SAE was identified as being directly treatment-related.

Table 3: Adverse events of the Orenstein 2009 study comparing lansoprazole to placebo

	Lansoprazole double blind (n=81)	Placebo double blind (n=81)	P value*	Lanzoprazole open label (n=55)	RRI	ARI	NNH
AE collection weeks, median, range¶	8.3, 1-9	8.3, 1-9	NS	7.3, 5-8	-	-	-
AE	50 (62%)	17 (21%)	NS (p=0.058)	11 (20%)	35%	16%	7
SAEs	10 (12%)	2 (2%)	0.032	2 (4%)	5%	10%	10

NS, not significant; RRI, relative risk increase; ARI, absolute risk increase; NNH, numbers needed to harm

*Double blind treatment comparisons: Fisher exact test for AE percentage; Wilcoxon test for weeks of AE collection

¶For the double blind period, “collection weeks” includes 30 days posttreatment for those subjects who did not enter open label treatment. For open label period this includes 20 days posttreatment for all subjects who entered open-label treatment.

The outcomes measures in the Moore 2003 study were cry fuss time in minutes/24 hours and a parental visual analog score. Results are shown in Tables 4 and 5. Period 1 and period 2 denotes the first two weeks and second two weeks of the trial, respectively. There was no significant difference in the cry/fuss time while taking either omeprazole or placebo (191 vs. 200, $P=0.400$), nor was there a significant difference in cry/fuss time between period 1 and 2 ($P=0.330$). There was a significant decrease in cry/fuss time from baseline to period 1 (267 vs. 203, $P=0.040$) and from baseline to period 2 (267 vs. 188, $P=0.008$). In an analysis of treatment order (subjects who initiated with omeprazole vs. subjects who initiated with placebo group) there was no difference in cry/fuss time from baseline ($P=0.481$), period 1 ($P=0.604$), or period 2 ($P=0.534$).

The visual analog device was a double sided slide rule with the side facing the parent showing two extremes of “no irritability” and “worst irritability” and the side facing the

investigator showing a linear scale of 0 to 10. The VA score while taking omeprazole or placebo was not significantly different (5.0 vs. 5.9, $P=0.214$). While there was not a remarkable decrease in the VA score between baseline and period 1 or between period 1 and 2, there was a significant decrease between baseline and period 2 (6.8 vs. 4.8, $P=0.008$). In an analysis of treatment order, there was no significant difference in VA score from baseline ($P=0.262$), period 1 ($P=0.724$), or period 2 ($P=0.105$). The data provided in Moore 2003 study is on a continuous scale and could not be converted dichotomously to directly answer whether or not there was a treatment effect.

Table 4: Cry fuss data in response to treatment with omeprazole or placebo, Moore 2003

Cry fuss time in min/24 hr (mean \pm SD)				
	Baseline	Period 1	Period 2	Combined*
Omeprazole (n=15)	246 \pm 105	203 \pm 113	179 \pm 129	191 \pm 120
Placebo (n=15)	287 \pm 132	204 \pm 87	198 \pm 115	201 \pm 100
Total (n=30)	267 \pm 119	203 \pm 99	188 \pm 121	

*Mean of the combined data from Period 1 and Period 2 (n=30)

Baseline vs. Period 1, $P=0.040$

Baseline vs. Period 2, $P=0.008$

Table 5: Visual analog score by parents of the level of infant irritability in response to treatment with omeprazole or placebo, Moore 2003

Visual analogue scale of infant irritability (mean \pm SD)				
	Baseline	Period 1	Period 2	Combined*
Omeprazole (n=15)	7.1 \pm 1.4	5.9 \pm 2.6	4.0 \pm 3.3	5.0 \pm 3.1
Placebo (n=15)	6.6 \pm 1.7	6.0 \pm 2.1	5.7 \pm 2.2	5.9 \pm 2.1
Total (n=30)	6.8 \pm 1.6	6.0 \pm 2.3	4.8 \pm 2.9	

*Mean of the combined data from Period 1 and Period 2 (n=30)

Baseline vs. Period 2, $P=0.008$

The Omari 2007 study demonstrated through esophageal pH monitoring that omeprazole therapy significantly reduced gastric acidity, esophageal acid exposure and the number and duration of acid reflux episodes compared to placebo³. However, the PPI did not demonstrate a significant change in the number of symptomatic events that are attributed to GER, as illustrated in Table 6. The treatment effect cannot be calculated based on the continuous data that was given.

Table 6: Effect of omeprazole on GER symptoms in preterm infants, Omari 2007

Symptoms	Frequency (number of events)	
	Placebo week	Omeprazole week
Vomiting	8.5 (7, 22.8)	6.5 (3, 14.3)
Apnea	0.4 (0, 1.5)	1 (0, 1.8)
Bradycardia	7.5 (1.3, 17.3)	6.5 (3, 16)
Choking	0 (0, 1)	0 (0, 1.8)
Behavioral changes	17 (8.3, 27.8)	16.5 (7.3, 30.1)

Data is presented as mean \pm SEM or median (interquartile range).

DISCUSSION

Proton pump inhibitors have attained the FDA approval for children one year and older and adults for short term treatment of symptomatic GERD and healing and symptomatic relief of all grades of erosive esophagitis. The only contraindication is sensitivity to prior PPIs or any component of the medication. The many available forms of PPIs include as a prescription, generic, and over the counter medication, such as Prevacid OTC (lansoprazole). PPIs have recently been in the medical news for their possible interactions with clopidogrel and the possible increase risk of fractures of hip, wrist, and spine; however, these circumstances do not directly apply to a patient population of infants. Pediatric Lexicomp Online states the uses and possible doses of lansoprazole for infants beginning at three months of age. Most importantly, Lexicomp found it necessary to note that treatment of GERD in children less than twelve months old is controversial based on the findings of the Orenstein 2009 trial.

There were noteworthy limitations to these studies. Firstly, crying is nonspecific to GERD; the coexistence of crying and reflux does not establish a causal relation. Behaviors that are thought to be reflux related also occur in infants independent of acid reflux episodes. Secondly, there may have been some variability with the outcomes data. Although all three studies' outcomes were concerned with the subjects' reduction of symptoms, they were

measured and recorded differently. It would have proven to be a more accurate comparison of the three studies if the outcomes were measured identically. For example, Orenstein 2009 study dealt with responder status and adverse events while Omari 2007 focused on symptoms observed and documented by nursing staff. Additionally, limitations regarding treatment could have included dosing, duration, or appropriate target. Orenstein 2009 study allowed subjects to enter an open label treatment after only one week of double blind treatment, which may have decreased the double blind response rate. Similarly, Omari 2007 subjects were only on the PPI and placebo for one week each while Moore 2005 trial lasted 4 weeks.

Finally the Moore 2005 study suggested that infant irritability can improve with time, independent of treatment. For both the cry/fuss time and VA score there was a significant decrease between baseline and period 2. If the primary mechanism for reflux in an infant is transient relaxation of lower esophageal sphincter, then it would be logical to postulate that as the muscle tone of sphincter increases with age, the symptoms of GERD should subside.

CONCLUSION

Proton pump inhibitors are not a safe and effective treatment for gastroesophageal reflux disease in infants less than 12 months old. Although the PPIs may have reduced the gastric and esophageal acidity, none of the trials showed a reduction in symptoms such as crying and irritability. In addition, placing infants on PPIs may put them at increased risk for adverse events. Future trials are warranted to investigate the primary cause of reflux symptoms in infants. It would be interesting to perform manometry of the lower esophageal sphincter to determine if relaxation of the sphincter can be attributed for the reflux. Serial esophageal manometry could establish if the strength of the sphincter increases with age and development, resulting in reduction of symptoms of GERD.

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